

**Amendment to the Claims:**

The listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. ( Twice Amended) A mouse model ~~non-human animal~~ being unresponsive to bacterial cell components, which is unresponsive to a lipoprotein/lipopeptide as a bacterial cell component by disruption of either TLR2 gene or MyD88 gene.
2. (Twice Amended) The mouse model ~~non-human animal~~ being unresponsive to bacterial cell components according to claim 1, wherein a lipoprotein/lipopeptide is a macrophage-activating lipopeptide obtained from bacteria which belong to Mycoplasma.
3. (Three Times Amended) The mouse model ~~non-human animal~~ being unresponsive to bacterial cell components according to claim 1, wherein the mouse model ~~non-human animal~~ is unresponsive to peptidoglycan as a bacterial cell component.
4. (Twice Amended) The mouse model ~~non-human animal~~ being unresponsive to bacterial cell components according to claim 1, wherein the mouse model ~~non-human animal~~ is hyporesponsive to a cell wall fraction of Gram-positive bacteria.
5. (Three Times Amended) The mouse model ~~non-human animal~~ being unresponsive to bacterial cell components according to claim 1, wherein the mouse model ~~non-human animal~~ is unresponsive to endotoxin as a bacterial cell component by the disruption of TLR4 gene.
6. (Three Times Amended) The mouse model ~~non-human animal~~ being unresponsive to bacterial cell components according to claim 1, wherein the mouse model ~~non-human animal~~ is

unresponsive to lipoteichoic acid as a bacterial cell component by the disruption of TLR4 gene.

7. (Three Times Amended) The mouse model ~~non-human animal~~ being unresponsive to bacterial cell components according to claim 1, wherein the mouse model ~~non-human animal~~ is unresponsive to Mycobacterium tuberculosis lysate as a bacterial cell component by the disruption of TLR4 gene.

8. (Withdrawn) The model non-human animal being unresponsive to bacterial cell components characterized by that the model non-human animal being unresponsive to bacterial cell components according to claim 1 is a non-human animal whose function of TLR2 gene is deficient on its chromosome.

9. (Withdrawn) The model non-human animal being unresponsive to bacterial cell components characterized by that the model non-human animal being unresponsive to bacterial cell components according to claim 1 is a non-human animal whose function of MyD88 gene is deficient on its chromosome.

10. (cancelled)

11. (cancelled)

12. (Withdrawn) A screening method of a suppressor or a promoter of responsiveness to bacterial cell components characterized in comprising the steps of: macrophages or splenocytes obtained from the non-human animal being unresponsive to bacterial cell components according to claim 1 and a subject material are brought into contact in advance in vitro; the macrophages or the splenocytes are cultured in the presence of bacterial cell components; the macrophage activity level or the splenocyte activity level of the macrophages or of the splenocytes is

measured and assessed.

13. (Withdrawn) A screening method of a suppressor or a promoter of responsiveness to bacterial cell components characterized in comprising the steps of: macrophages or splenocytes obtained from the non-human animal being unresponsive to bacterial cell components according to claim 1 and bacterial cell components are brought into contact in advance in vitro; the macrophages or the splenocytes are cultured in the presence of a subject material; the macrophage activity level or the splenocyte activity level of the macrophages or of the splenocytes is measured and assessed.

14. (Withdrawn) A screening method of a suppressor or a promoter of responsiveness to bacterial cell components characterized in comprising the steps of: a subject material is administered in advance to the non-human animal being unresponsive to bacterial cell components according to claim 1; macrophages or splenocytes obtained from the non-human animal are cultured in the presence of bacterial cell components; the macrophage activity level or the splenocyte activity level of the macrophages or of the splenocytes is measured and assessed.

15. (Withdrawn) A screening method of a suppressor or a promoter of responsiveness to bacterial cell components characterized in comprising the steps of: a subject material is administered in advance to the non-human animal being unresponsive to bacterial cell components according to claim 1; the non-human animal is made to be infected with bacteria; the macrophage activity level or the splenocyte activity level of the macrophages or of the splenocytes obtained from the non-human animal is measured and assessed.

16. (Withdrawn) A screening method of a suppressor or a promoter of responsiveness to bacterial cell components characterized in comprising the steps of: the non-human animal being unresponsive to bacterial cell components according to claim 1 is made to be infected with

bacteria in advance; macrophages or splenocytes obtained from the non-human animal are cultured in the presence of a subject material; the macrophage activity level or the splenocyte activity level of the macrophages or of the splenocytes is measured and assessed.

17. (Withdrawn) A screening method of a suppressor or a promoter of responsiveness to bacterial cell components characterized in comprising the steps of: the non-human animal being unresponsive to bacterial cell components according to claim 1 is made to be infected with bacteria in advance; a subject material is administered to the non-human animal; the macrophage activity level or the splenocyte activity level of the macrophages or of the splenocytes obtained from the non-human animal is measured and assessed.

18. (Withdrawn) A screening method of a suppressor or a promoter of responsiveness to bacterial cell components characterized in comprising the steps of: a subject material is administered in advance to the non-human animal being unresponsive to bacterial cell components according to claim 1; the non-human animal is made to be infected with bacteria; the macrophage activity level or the splenocyte activity level of the macrophages or of the splenocytes in the non-human animal is measured and assessed.

19. (Withdrawn) A screening method of a suppressor or a promoter of responsiveness to bacterial cell components characterized in comprising the steps of: the non-human animal being unresponsive to bacterial cell components according to claim 1 is made to be infected with bacteria in advance; a subject material is administered to the non-human animal; the macrophage activity level or the splenocyte activity level of the macrophages or of the splenocytes in the non-human animal is measured and assessed.

20. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein those levels are assessed in

comparison to the measured value of a wild type non-human animal as control, which is the same species of the nonhuman animal being unresponsive to bacterial cell components, in the measurement and the assessment of the macrophage activity level or the splenocyte activity level.

21. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the measurement and the assessment of the macrophage activity level is the measurement and the assessment of the production amount of cytokine and/or nitrous ion in the macrophage.

22. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the measurement and the assessment of the splenocyte activity level is the measurement and the assessment of the expression amount of MHC class II in the splenocyte.

23. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the bacterial cell component is a lipoprotein/lipopeptide.

24. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 23, wherein the lipoprotein/lipopeptide is derived from cell components of bacteria which belong to Mycoplasma, Spirochaeta, Escherichia or the like.

25. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the bacterial cell component is peptidoglycan.

26. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the bacterial cell component is endotoxin.

27. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the bacterial cell component is lipoteichoic acid.

28. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the bacterial cell component is *Mycobacterium tuberculosis* lysate.

29. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the suppressor or the promoter of responsiveness to bacterial cell components is a suppressor or a promoter of bacterial infection.

30. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the suppressor or the promoter of responsiveness to bacterial cell components is an agonist or an antagonist of TLR2.

31. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the suppressor or the promoter of responsiveness to bacterial cell components is a suppressor or a promoter of interleukin-1 activity.

32. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to

bacterial cell components according to claim 12, wherein the suppressor or the promoter of responsiveness to bacterial cell components is a suppressor or a promoter of interleukin-18 activity.

33. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the suppressor or the promoter of responsiveness to bacterial cell components is a suppressor or a promoter of IFN- $\gamma$  activity.

34. (Withdrawn) The screening method of a suppressor or a promoter of responsiveness to bacterial cell components according to claim 12, wherein the suppressor or the promoter of responsiveness to bacterial cell components is a suppressor or a promoter of TNF- $\alpha$  activity.

35. (Withdrawn) A suppressor or a promoter of responsiveness to bacterial cell components characterized in being obtainable by the screening method of a suppressor or a promoter of responsiveness to bacterial cell components according claim 12.

36. (Withdrawn) the suppressor or the promoter of responsiveness to bacterial cell components according to claim 35, wherein the suppressor or the promoter of responsiveness to bacterial cell components is a suppressor or a promoter of bacterial infection.

37. (Withdrawn) The suppressor or the promoter of responsiveness to bacterial cell components according to claim 35, wherein the suppressor or the promoter of responsiveness to bacterial cell components is an agonist or an antagonist of TLR2.

38. (Withdrawn) An assessing method of a subject material characterized in comprising the steps of: the subject material is administered to the non-human animal being unresponsive to bacterial cell components according to claim 1; the bioactivity of the subject material is assessed.

39. (Withdrawn) An assessing method of a subject material characterized in comprising the steps of: the subject material is administered to the non-human animal being unresponsive to bacterial cell components according to claim 1 and to a wild-type non-human animal of the non-human animal respectively; the bioactivity of each subject material is compared and assessed.

40. (Withdrawn) The assessing method of a subject material according to claim 38, wherein the bioactivity is an endotoxin activity.

41. (Withdrawn) The assessing method of a subject material according to claim 38, wherein the bioactivity is an interleukin-1 activity.

42. (Withdrawn) The assessing method of a subject material according to claim 38, wherein the bioactivity is an interleukin-18 activity.

43. (Withdrawn) A method of detecting bacterial cell components characterized in comprising the steps of: a subject material is administered to the non-human animal being unresponsive to bacterial cell components according to claim 1; bacterial cell components in the subject material are detected.

44. (Withdrawn) A method of detecting bacterial cell components characterized in comprising the steps of: the subject material is administered to the non-human animal being unresponsive to bacterial cell components according to claim 1 and to a wild-type non-human animal of the non-human animal respectively; bacterial cell components in the subject materials are detected.

45. (Withdrawn) The method of detecting bacterial cell components according to claim 43, wherein the bacterial cell component is a lipoprotein/lipopeptide.



46. (Withdrawn) the method of detecting bacterial cell components according to claim 45, wherein the lipoprotein/lipopeptide is derived from cell components of bacteria which belong to Mycoplasma, Spirochaeta, Escherichia or the like.

47. (Withdrawn) The method of detecting bacterial cell components according to claim 43, wherein the bacterial cell component is peptidoglycan.

48. (Withdrawn) The method of detecting bacterial cell components according to claim 43, wherein the bacterial cell component is endotoxin.

49. (Withdrawn) The method of detecting bacterial cell components according to claim 43, wherein the bacterial cell component is lipoteichoic acid.

50. (Withdrawn) A TLR2 knockout mouse characterized in being obtainable by a process comprising the steps of: a targeting vector is constructed by replacing a whole or a part of a gene fragment of an exon region containing a cytoplasmic region of TLR2 gene obtained by screening a mouse genomic library with a probe derived from a mouse EST clone with a plasmid having a poly A signal and a marker gene; the targeting vector is linearized and then introduced into an embryonic stem cell; chimeric mice are generated by microinjecting the targeting ES cells whose function of TLR2 gene is deficient into the blastocysts of mice; heterozygous mice are generated by mating the chimeric mice and wild-type mice; the heterozygous mice are intercrossed.

51. (Withdrawn) An MyD88 knockout mouse characterized in being obtainable by a process comprising the steps of: a targeting vector is constructed by replacing a whole or a part of a gene fragment of two exon regions encoding a C-terminal portion of MyD88 gene region obtained by screening a mouse genomic library with a probe derived from a mouse EST clone with a plasmid

Appl. No. 09/889,324  
Amendment dated December 29, 2003  
Reply to Office Action of July 29, 2003

having a poly A signal and a marker gene; the targeting vector is linearized and then introduced into the embryonic stem cell; chimeric mice are generated by microinjecting the targeting ES cells whose function of MyD88 gene is deficient into the blastocysts of mice; heterozygous mice are generated by mating the chimeric mice and wild-type mice; the heterozygous mice are intercrossed.